

WHAT IS CLAIMED IS:

1. An isolated and purified urocortin III protein
selected from the group consisting of human urocortin III and mouse
5 urocortin III.

2. The isolated and purified urocortin III protein of
claim 1, wherein said protein is mouse urocortin III derived from a
10 precursor peptide of amino acid sequence SEQ ID No: 4.

3. The isolated and purified urocortin III protein of
claim 1, wherein said protein is mouse urocortin III having amino
15 acid sequence SEQ ID No: 5.

4. The mouse urocortin III protein of claim 3, wherein
the N-terminal end of said protein is modified with acylating agents
20 selected from the group consisting of carboxyl-containing moieties,
sulfonyl-containing moieties and isocyanates.

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5. The mouse urocortin protein of claim 3, wherein the N-terminal end of said protein is extended with additional amino acids or peptides selected from the group consisting of D-tyrosine, L-tyrosine, D-tyrosine-glycine, and L-tyrosine-glycine.

6 The mouse urocortin III protein of claim 3, wherein the N-terminal end of said protein is chemically crosslinked to a toxin molecule.

7. The mouse urocortin III protein of claim 3, wherein the N-terminal end of said protein is extended with additional amino acids or peptides selected from the group consisting of D-iodotyrosine, L-iodotyrosine, D-iodotyrosine-glycine, and L-iodotyrosine-glycine and wherein methionine residues at positions 12 and 35 are replaced with Nle.

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8. The mouse urocortin III protein of claim 7, wherein the iodotyrosine residue is labeled with an ^{125}I radioisotope.

5 9. A CRF-R2 antagonist comprising the mouse urocortin III protein of claim 3 with an N-terminal deletion selected from the group consisting of the first five amino acids, the first six amino acid, the first seven amino acids, and the first eight amino acids.

10 10. A pharmaceutical composition comprising the CRF-R2 antagonist of claim 9 and a pharmaceutically acceptable carrier.

15 11. A method of treating a pathophysiological state, comprising the step of administering the pharmaceutical composition of claim 10 to an individual in need of such treatment.

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12. The method of claim 11 wherein said pathophysiological state is selected from the group consisting of congestive heart failure, vascular disease, gastrointestinal dysfunction, diabetes mellitus and migraine headaches.

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13. A method of inhibiting angiogenesis, comprising the step of administering the pharmaceutical composition of claim 10 to an individual in need of such treatment.

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14. The CRF-R2 antagonist of claim 9 wherein the N-terminal end of said antagonist is blocked with an acylating agent selected from the group consisting of carboxyl-containing moieties, sulfonyl-containing moieties and isocyanates.

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15. A pharmaceutical composition comprising the CRF-R2 antagonist of claim 14 and a pharmaceutically acceptable carrier.

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16. A method of treating a pathophysiological state, comprising the step of administering the pharmaceutical composition of claim 15 to an individual in need of such treatment.

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17. The method of claim 16 wherein said pathophysiological state is selected from the group consisting of congestive heart failure, vascular disease, gastrointestinal dysfunction, diabetes mellitus and migraine headaches.

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18. A method of inhibiting angiogenesis, comprising the step of administering the pharmaceutical composition of claim 15 to an individual in need of such treatment.

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19. A synthetic urocortin III analog comprising the mouse urocortin III protein of claim 3, wherein said protein contains one or more amino acid substitutions selected from the group consisting of Ile₃, Nle₃, C_αMe-Leu₃, Ile₅, Nle₅, C_αMe-Leu₅, Leu₇, Nle₇, Thr₈, Ile₉, Phe₉, Gly₁₀, His₁₀, Leu₁₁, Nle₁₁, Leu₁₂, Nle₁₂, Arg₁₃, Gln₁₃,

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Nle₁₄, C_αMe-Leu₁₄, Nle₁₅, C_αMe-Leu₁₅, C_αMe-Leu₁₆, Leu₁₆, Nle₁₆, Glu₁₇,
Asp₁₇, Nle₁₈, Leu₁₈, Arg₂₀, Nle₂₄, C_αMe-Leu₂₄, Arg₃₂, Ile₃₄, Nle₃₄, C_αMe-
Leu₃₄, Leu₃₅, Nle₃₅, Asp₃₆, Glu₃₆ and Val₃₈.

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20. The synthetic urocortin III analog of claim 19,
wherein a methionine residue at position 12 is replaced with Nle.

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21. The synthetic urocortin III analog of claim 19,
wherein a methionine residue at position 35 is replaced with Nle.

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22. A pharmaceutical composition comprising the
synthetic urocortin III analog of claim 19 and a pharmaceutically
acceptable carrier.

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23. A method of treating a pathophysiological state,
comprising the step of administering the pharmaceutical composition
of claim 22 to an individual in need of such treatment.

24. The method of claim 23, wherein said pathophysiological state is selected from the group consisting of high body temperature, appetite dysfunction, congestive heart failure, vascular disease, gastrointestinal dysfunction, stress, undesirably low
5 levels of glucagon secretion or activity and anxiety.

25. A CRF-R2 antagonist comprising the synthetic urocortin III analog of claim 19 with an N-terminal deletion selected
10 from the group consisting of the first five amino acids, the first six amino acid, the first seven amino acids, and the first eight amino acids.

26. A pharmaceutical composition comprising the CRF-
15 R2 antagonist of claim 25 and a pharmaceutically acceptable carrier.

27. A method of treating a pathophysiological state,
20 comprising the step of administering the pharmaceutical composition of claim 26 to an individual in need of such treatment.

28. The method of claim 27 wherein said pathophysiological state is selected from the group consisting of congestive heart failure, vascular disease, gastrointestinal dysfunction, diabetes mellitus and migraine headaches.

29. A method of inhibiting angiogenesis, comprising the step of administering the pharmaceutical composition of claim 26 to an individual in need of such treatment.

30. The CRF-R2 antagonist of claim 25 wherein the N-terminal end of said antagonist is blocked with an acylating agent selected from the group consisting of carboxyl-containing moieties, sulfonyl-containing moieties and isocyanates.

31. A pharmaceutical composition comprising the CRF-R2 antagonist of claim 29 and a pharmaceutically acceptable carrier.

32. A method of treating a pathophysiological state, comprising the step of administering the pharmaceutical composition of claim 31 to an individual in need of such treatment.

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33. The method of claim 32 wherein said pathophysiological state is selected from the group consisting of congestive heart failure, vascular disease, gastrointestinal dysfunction, diabetes mellitus and migraine headaches.

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34. A method of inhibiting angiogenesis, comprising the step of administering the pharmaceutical composition of claim 31 to an individual in need of such treatment.

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35. The isolated and purified urocortin III protein of claim 1, wherein said protein is human urocortin III derived from a precursor peptide of amino acid sequence SEQ ID No: 2.

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36. The isolated and purified urocortin III protein of claim 35, wherein said protein is human urocortin III having amino acid sequence SEQ ID No: 3.

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37. The human urocortin III protein of claim 36 containing at least one amino acid substitution selected from the group consisting of Ile₁₄, Asp₁₉, Lys₂₇, and Gln₃₃ or a combination thereof.

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38. The human urocortin III protein of claim 37, wherein said protein contains a single amino acid substitution consisting of Ile₁₄.

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39. The human urocortin III protein of claim 36, wherein the N-terminus of said protein is extended with an acylating agent selected from the group consisting of carboxyl-containing moieties, sulfonyl-containing moieties and isocyanates.

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40. The human urocortin III protein of claim 36, wherein the N-terminal end of said protein is extended with additional amino acids or peptides selected from the group consisting of D-tyrosine, L-tyrosine, D-tyrosine-glycine, and L-tyrosine-glycine.

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41. The human urocortin III protein of claim 36, wherein the N-terminal end of said protein is chemically crosslinked to a toxin molecule.

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42. The human urocortin III protein of claim 36, wherein the N-terminal end of said protein is extended with additional amino acids or peptides selected from the group consisting of D-iodotyrosine, L-iodotyrosine, D-iodotyrosine-glycine, and L-iodotyrosine-glycine and wherein methionine residues at positions 12 and 35 are replaced with Nle.

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43. The human urocortin III protein of claim 41, wherein the iodotyrosine residue is labeled with an ^{125}I radioisotope.

44. A CRF-R2 antagonist comprising the human urocortin III protein of claim 36 with an N-terminal deletion selected from the group consisting of the first five amino acids, the first six amino acid, the first seven amino acids, and the first eight amino acids.

45. A pharmaceutical composition comprising the CRF-R2 antagonist of claim 44 and a pharmaceutically acceptable carrier.

46. A method of treating a pathophysiological state, comprising the step of administering the pharmaceutical composition of claim 45 to an individual in need of such treatment.

47. The method of claim 46 wherein said pathophysiological state is selected from the group consisting of congestive heart failure, vascular disease, gastrointestinal dysfunction, diabetes mellitus and migraine headaches.

48. A method of inhibiting angiogenesis, comprising the step of administering the pharmaceutical composition of claim 45 to an individual in need of such treatment.

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49. A CRFR2 antagonist comprising the CRF-R2 antagonist of claim 44 wherein the N-terminal end of said antagonist is blocked with an acylating agent selected from the group consisting of carboxyl-containing moieties, sulfonyl-containing moieties and isocyanates.

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50. A pharmaceutical composition comprising the CRF-R2 antagonist of claim 49 and a pharmaceutically acceptable carrier.

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51. A method of treating a pathophysiological state, comprising the step of administering the pharmaceutical composition of claim 50 to an individual in need of such treatment.

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52. The method of claim 51 wherein said pathophysiological state is selected from the group consisting of congestive heart failure, vascular disease, gastrointestinal dysfunction, diabetes mellitus and migraine headaches.

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53. A method of inhibiting angiogenesis, comprising the step of administering the pharmaceutical composition of claim 50 to an individual in need of such treatment.

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54. A synthetic urocortin III analog comprising the human urocortin III protein of claim 36, wherein said protein contains one or more amino acid substitutions selected from the group consisting of Ile₃, Nle₃, C_αMe-Leu₃, Ile₅, Nle₅, C_αMe-Leu₅, Leu₇, Nle₇, Thr₈, Ile₉, Phe₉, Gly₁₀, His₁₀, Leu₁₁, Nle₁₁, Leu₁₂, Nle₁₂, Arg₁₃, Gln₁₃, Nle₁₄, C_αMe-Leu₁₄, Nle₁₅, C_αMe-Leu₁₅, C_αMe-Leu₁₆, Leu₁₆, Nle₁₆, Glu₁₇, Asp₁₇, Nle₁₈, Leu₁₈, Arg₂₀, Nle₂₄, C_αMe-Leu₂₄, Arg₃₂, Ile₃₄, Nle₃₄, C_αMe-Leu₃₄, Leu₃₅, Nle₃₅, Asp₃₆, Glu₃₆, and Val₃₈.

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55. The urocortin III analog of claim 54, wherein a methionine residue at position 12 is replaced with Nle.

5 56. The urocortin III analog of claim 54, wherein a methionine residue at position 35 is replaced with Nle.

10 57. A pharmaceutical composition comprising the urocortin III analog of claim 54 and a pharmaceutically acceptable carrier.

15 58. A method of treating a pathophysiological state, comprising the step of administering the pharmaceutical composition of claim 57 to an individual in need of such treatment.

20 59. The method of claim 58, wherein said pathophysiological state is selected from the group consisting of high body temperature, appetite dysfunction, congestive heart failure,

vascular disease, gastrointestinal dysfunction, stress, undesirably low levels of glucagon secretion or activity and anxiety.

5 60. A CRF-R2 antagonist comprising the human urocortin III analog of claim 54 with an N-terminal deletion selected from the group consisting of the first five amino acids, the first six amino acid, the first seven amino acids, and the first eight amino acids.

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61. A pharmaceutical composition comprising the CRF-R2 antagonist of claim 60 and a pharmaceutically acceptable carrier.

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62. A method of treating a pathophysiological state, comprising the step of administering the pharmaceutical composition of claim 61 to an individual in need of such treatment.

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63. The method of claim 62 wherein said pathophysiological state is selected from the group consisting of congestive heart failure, vascular disease, gastrointestinal dysfunction, diabetes mellitus and migraine headaches.

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64. A method of inhibiting angiogenesis, comprising the step of administering the pharmaceutical composition of claim 61 to an individual in need of such treatment.

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65. The CRF-R2 antagonist of claim 60 wherein the N-terminal end of said antagonist is blocked with an acylating agent selected from the group consisting of carboxyl-containing moieties, sulfonyl-containing moieties and isocyanates.

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66. A pharmaceutical composition comprising the CRF-R2 antagonist of claim 65 and a pharmaceutically acceptable carrier.

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67. A method of treating a pathophysiological state, comprising the step of administering the pharmaceutical composition of claim 66 to an individual in need of such treatment.

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68. The method of claim 67 wherein said pathophysiological state is selected from the group consisting of congestive heart failure, vascular disease, gastrointestinal dysfunction, diabetes mellitus and migraine headaches.

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69. A method of inhibiting angiogenesis, comprising the step of administering the pharmaceutical composition of claim 66 to an individual in need of such treatment.

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70. The urocortin III protein of claim 1, wherein said protein has been modified to contain a molecular label.

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71. The protein of claim 70, wherein said label is selected from the group consisting of fluorescent labels, photoaffinity labels and radioactive markers.

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72. A method of determining whether a cell has urocortin III receptors, comprising the steps of:

incubating said cells with the urocortin III protein of claim 70,

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detecting said molecular label, wherein the presence of said label on said cells indicates that said cells have urocortin III receptors.

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73. A conjugate of the protein of claim 1 linked to a toxin.

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74. An antibody directed against the urocortin III protein of claim 1.

75. The antibody of claim 74, wherein said antibody is a monoclonal antibody.

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76. The antibody of claim 74 conjugated to a molecular label.

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77. The antibody of claim 76, wherein said label is selected from the group consisting of fluorescent labels, photoaffinity labels and radioactive markers.